# Non-clinical Cardiovascular Safety Testing: Moving Forward

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### **Disclosure Statement**

I have no financial relationships with proprietary entities that produce health care goods and services

The opinions and information in this presentation are my own and do not necessarily reflect the views and policies of the FDA

#### **Outline**

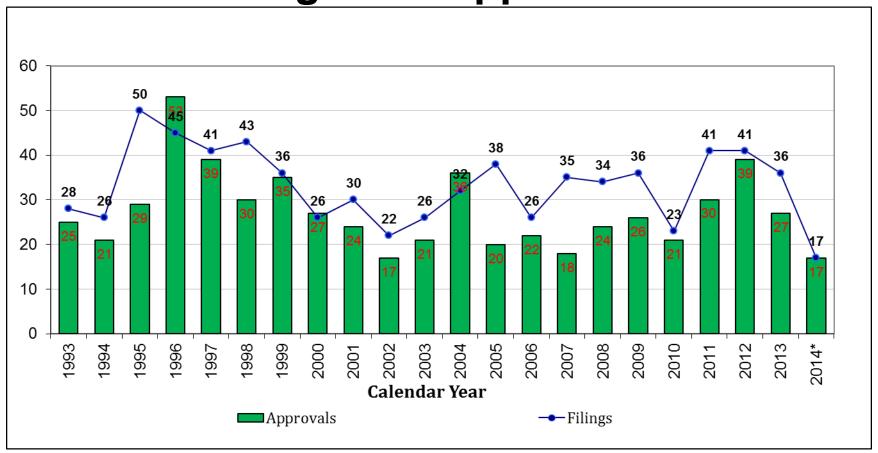
- Need for Efficient Drug Development
- Challenge of Cardiovascular Toxicity in Drug Development
- Promise of Non-Clinical Models to Replace Clinical Testing

### **Central Message**

- Optimization of drug development requires
  - Broad stakeholder interaction between regulators, academics and industry
  - Ongoing willingness to test our current testing paradigms and look for more efficient approaches without lowering our standards for safety
  - Non-clinical modeling of cardiovascular toxicity promising area of research

# Challenge of Efficient Drug Development

### CDER NME NDAs/BLAs<sup>†</sup> Filings and Approvals



Data as of 6/30/2014

<sup>†</sup> Multiple applications pertaining to a single new molecular/biologic entity (e.g. single ingredient and combinations) are only counted once. Therefore, the numbers represented here for CY14 filings are not indicative of workload in the PDUFA V Program.

<sup>†</sup> Original BLAs that do not contain a new active ingredient are excluded

<sup>\*</sup>Since applications are received and filed throughout a calendar year, the filed applications in a given calendar year do not necessarily correspond to an approval in the same calendar year. Certain applications are within their 60-day filing review period and may not be filed upon completion of the review.

# Challenge of Cardiac Toxicity in Drug Development

**Table I.** Leading reasons for drug withdrawal over the last 40 years 1,2

Worldwide withdrawal (121 compounds)

US Withdrawal (95 compounds)

Reason	Percent	Reason	Percent
Hepatotoxicity	26	Cardiovascular safety (proarrhythmia)	19 (12)
Hematologic toxicity	10	Neuropsychiatric effects	12
Cardiovascular safety	9	Hepatotoxicity	9
Dermatologic effects	6	Bone marrow toxicity	7
Carcinogenicity	6	Allergic reactions	6

American Heart Journal September 2009

# Challenge: Identifying Common Toxicities

QT-Interval Prolongation and Torsade de Pointes (TdP)



#### Drugs Removed From Market for Arrhythmia Risk

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• Encainide (Enkaid®) 1991 (1986)*
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- Terfenadine (Seldane®) 1998 (1985)
- Astemizole (Hismanal®) 1999 (1988)
- Grepafloxacin (Raxar®) 1999 (1997)
- Cisapride (Propulsid®) 2000 (1993)
- Levomethadyl (Orlaam®) 2003 (1993)

<sup>\*</sup> year of removal (year of approval)



### Responses to Drug-induced TdP

- Regulatory
  - ICH S7B, E14guidances
  - FDA QTinterdisciplinaryreview team
- Technical
  - HL7 ECG data standard
  - ECG Warehouse

- Community & Research
  - Specialized QT study vendors
  - ECG MetricsConsortium
  - Cardiac SafetyResearchConsortium



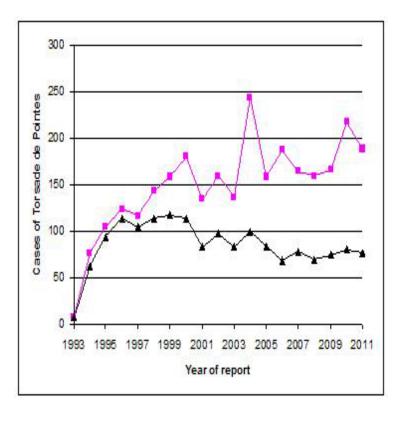
#### **Direct costs**

- Since 2005
  - Around 300 Through QT ('TQT') studies reported to FDA
  - Estimated 450 TQT studies performed
  - Estimated cost per study is few\$M
- Total of ~\$1B over 9 years



### **Impact**

- No new drug withdrawals
- Decline in TdP as a reported adverse event



All drugs

Excluding anti-arrhythmics

### Challenge: Identifying New Cardiovascular Toxicities

## Other Reported Drug-Induced Cardiovascular Toxicity

- Tyrosine Kinase Inhibitor\* cardio-toxicity:
  - Reduced myocardial contractility, CHF
  - Hypertension
  - QT prolongation
- Antibody pro-thrombotic effects
  - Bevacizimab, Ponatinib

### Challenge: Efficient Development

- Identify safety signals early and accurately wherever possible
- Monitor for unanticipated or incompletely characterized cardiovascular toxicities after approval

 Additional important goal: reduce, replace and refine use of animals

### Meeting These Challenges: Role of Non-Clinical Testing

### QT as and Example: Changing the Paradigm

- E14 and S7B have allowed us to avoid additional drug withdrawals
  - Clinical testing paradigm (TQT studies)
    carries additional cost in \$\$ and time
- Can improved science provide alternative to TQT?

### **Reasons for Optimism**

- Basis for TdP is mechanistically well-understood and testable
  - Rooted in effects on individual ion channels
- Technology exists on a commercial scale to be able to test drug effects on isolated channels using high-throughput technology that is reasonably available
- Computational techniques exist to analyze data and model effects on proarrhythmic risk

# Comprehensive in vitro Proarrhythmia Assay (CiPA)

- Assess drug effects on each cardiac ion channel type individually, using a high-throughput assay
- Compute net effect on repolarization and risks for TdP
- Check to see if you missed something important
  - Action potentials in stem cell derived human cardiac myocytes
  - Signature of drug effects on the morphology of the ECG

### **CiPA Organization**

- Ion Channel Work Stream led by SPS/Fermini & Abi Gerges
- In Silico Work Stream led by FDA/Colatsky
- Myocyte Work Stream led by HESI/Gintant & Zhang
- Compound Selection Work Stream led by CSRC/Sager
- Steering Committee / above plus various academics and regulators at EMA, Japan, and FDA.

### **Progress note**

- Large international enterprise (pharma, technology vendors, academics, regulators) underway to define protocols
- Pilot studies getting underway
- Validation plan coordinated with various regulatory agencies and ICH groups
- Goal: initial analyses 18 months or so to assess progress

### Other Cardiovascular Toxicities

- Need for close monitoring as data accumulates for idiosyncratic and unanticipated toxicities
  - Chronic exposure particular challenge
- Toxicities with clear mechanisms of action potentially can follow pathway of QT prolongation
- Some toxicities (e.g., myocardial contractility) harder to test using cell-based systems
- Even where replacement of clinical testing proves impossible, non-clinical testing has a role in understanding mechanisms, reducing clinical testing and aiding work to prevent toxicities

### **Summary**

- Non-clinical testing to identify cardiovascular toxicity is important in drug development:
  - Identifying the toxicity early allows the sponsor to develop ways to prevent or mitigate a toxicity, or abandon a compound early
  - Characterizing toxicities identified late in development or during postmarketing
- Ongoing work to replace clinical testing with in vitro testing for QT interval prolongation provides a possible pathway for other well-understood toxicities
- FDA understands important role that efficient testing plays in drug development and use